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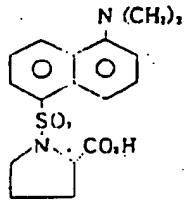
Detailed Description

1. Title of the Invention: Optical resolution method

2. Scope of the Claims

(1) Method of optical resolution of antipodal amines characterized in that antipodal amines are converted to their derivatives (amide compounds) by reacting with dansyl-L-proline shown by the below structure



and separating the derivatives by chromatography and detecting the separated components with fluorescence detector.

3. Detailed Description of Invention

Areas of industrial application

This invention relates to optical resolution of derivatized antipodal amines. This invention allows separation and isolation of optical antipodes of amines, especially amino acids and the like that are useful as drugs, food additives, and the raw materials thereof.

Conventional technology

Optical resolution of amines by reacting them with a chiral derivatizing reagent and separating the antipodes are known, for example, in publications such as J. Chromatogr., 152, (1978), 413; Anal. Chem., 59 (1987), 1191; and J. Chromatogr., 205 (1981), 325 (1981).

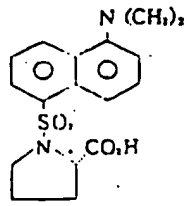
Problems to be solved by this invention

However, the conventional optical resolution method had problem of the derivatizing agents not being available in high purity and/or inexpensively and the types of target optical antipodes were limited.

Strategy for solving the problem

We the inventors have investigated diligently to solve the above problems of the conventional methods and found that optical resolution of derivatized amines is achieved

by converting antipodal amines to their derivatives (amide compounds) by reacting with chiral dansyl-L-proline (herein after DLP) shown by the below structure



and separating the derivatives by chromatography and detecting the separated components with fluorescence detector and thus arrived at this invention.

In the following, this invention is described with further detail.

The amine compounds applicable for the method of this invention include, for example, alanine, phenylalanine, α-amino-γ-butyrolactone, 2-amino-1-propanol, 1-amino-2-propanol, phenylethanolamine, N-methylphenylethanolamine, α-methylbenzylamine, norephedrin (RS), norpseudoephedrine (RR), 2-amino-1-butanol, sec-butylamine, 2-methylpiperidine, ephedrine, propranol [sic], and 3-mthylpiperidine, but the applicable amines are not limited to these.

The reaction of the amines and DLP (I) is effected, for example, by reacting the carboxyl group of DLP and amino group of the target amine in the presence of solvent such as N,N-dimethylformamide, dimethylacetamide, N-methylpyrolidone, acetamide, N,N-dietylformamide, and the like and optionally in the presence of diethylcyanophosphate (peptide condensing agent) and/or a base such as triethylamine and preferably under room temperature to form amides (derivatives).

The derivatives thus formed are obtained as diastereomers. The diastereomer mixture is then injected as is with the reaction solvents or after being isolated from the solvents into a chromatographic apparatus, preferably high performance liquid chromatography equipped with fluorescent detector (for example Shimadzu RF-535) to separate the optical antipode drivatives. The high performance liquid chromatography may be conducted, for example using a reverse-phase chromatography column such as Shimpack CLC-ODS (M) (Shimadzu Seisakusho). For the mobile phase, a mixed solvent system such as water/methanol or water/acetonitrile and the like is useful. The derivatives injected into the column are detected, for example, by the above described fluorescence detector. The separated derivatives (amides) are then converted to antipodal amines by a commonly known method, for example, hydrolysis in the presence of inorganic or organic acids.

Application Examples

This invention is further described with application examples below.

Application Example 1

A 0.2 mL of a 10 μM solution of DLP in N,N-dimethylformamide was added to 0.2 mL of 10 μM solution of optically antipodal amines in N,N-dimethylformamide. Then 0.1 mL each of diethylcyanophosphate solution (22 μM in N,N-dimethylformamide) and triethylamine (42 μM in N,N-dimethylformamide) were added and the resulting mixture was allowed to stand for 1 min.

Then the reaction aliquot was injected into a high performance liquid chromatography apparatus equipped with Simpack ODS (M) (4.6 mmi x 250 mm), eluted with water/methanol or water/acetonitrile at constant solvent composition, and the peaks were detected with a fluorescent detector (solvent flow rate 0.6~0.7 mL/min; column temperature 45oC; fluorescent detector excitation 515 nm, 345 nm). The column chromatogram of DLP derivatized DL-alanine is shown in Figure 1. The components of each peak were identified by LC/MS as the amides derivatized with DLP. The results of the high performance liquid chromatography analysis of other DLP drivatized amines were listed in Table 1.

Table 1: High Performance Liquid Chromatography Separation of Diastereomeric Amids Derived from Optically Antipodal Amines and DLP

Compounds	K[1)]	α[1)]	R_t[3)]	Cond.[4)]
Alanine[5)]	3.43 3.84	1.12	2.30	(A)
Phenylalanine[5)]	2.68 2.84 2.97	1.07	1.18	(B)
2-Amino-1-propanol	2.39 2.47	1.04	0.55	(C)
2-Amino-1-butanol	3.23 3.35	1.05	0.85	(C)
1-Amino-2-propanol	3.72 3.78	1.01	0.28	(D)
Phenylethanolamine	7.70 7.80	1.01	0.26	(D)
N-Methylphenylethanolamine	3.31 3.53	1.08	1.50	(A)
Norephedrine (RS) Norpseudoephedrine (RR)	6.98 7.36	1.06	1.50	(C)
α-Methylbenzylamine	3.55 3.66	1.04	0,78	(B)

1) Capacity Ratio ([same words in Japanese]); 2) Separation Factor
3) Resolution Value 4) Mobile Phase, (A)70% MeOH, (B) 80% MeOH
(C) 50% AcCN, (D) 60% MeOH; 5) Methyl ester

Effectiveness of the invention

The optical resolution method of this invention for resolving optically antipodal amines is found to be effective as indicated by the R_t values shown in Table 1.

4. Brief Description of the Figures

Figure 1 is a chromatogram of DLP derivatives of alanine (a) and phenylalanine (b).

(1)...Peak for L-alanine DLP derivative
(2)...Peak for D-alanine DLP derivative
(3)...Peak for L-phenylalanine DLP derivative
(4)...Peak for D-phenylalanine DLP derivative

Figure 2 is a chromatogram of DLP derivatives of phenylethanolamine and N-methylphenylethanolamine.

(1)...Peak for D,L-phenylethanolamine DLP derivative (unresolved)
(2)...Peak for L-methylphenylethanolamine [sic] DLP derivative
(3)...Peak for D-methylphenylethanolamine [sic] DLP derivative

Figure 3 is a chromatogram of DLP derivatives of norephedrine and norpseudoephedrine.

(1)...Peak for (1R, 2S)-norephedrine DLP derivative
(2)...Peak for (1R,2R)-norpseudoephedrine DLP derivative
(3)...Peak for (1S,2R)-norephedrine DLP derivative

Figure 1

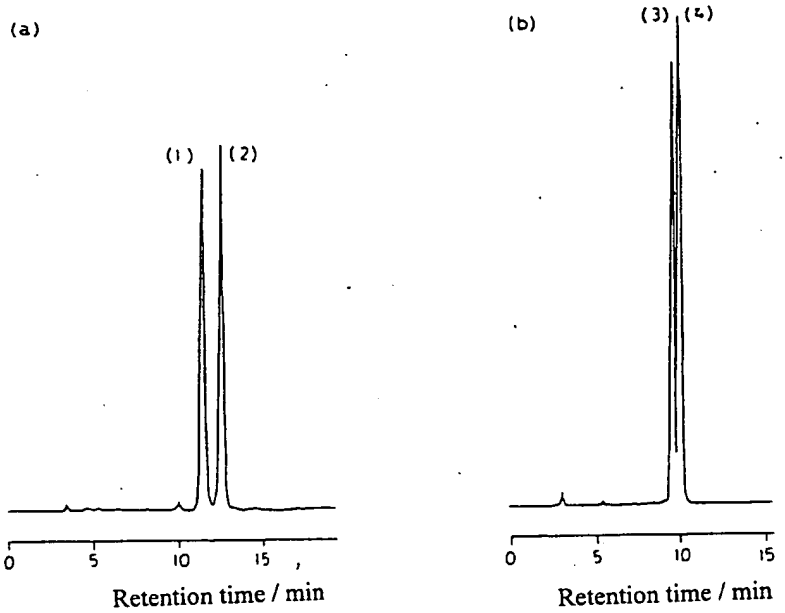


Figure 2

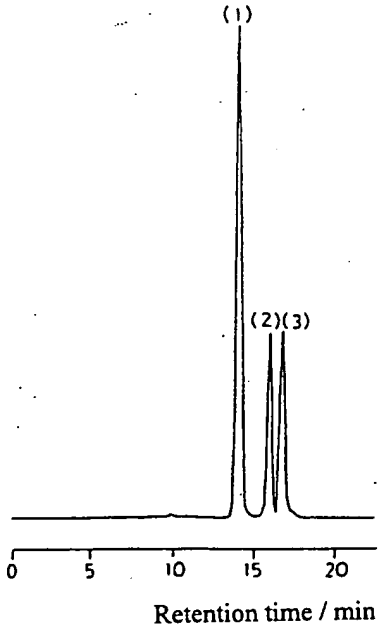
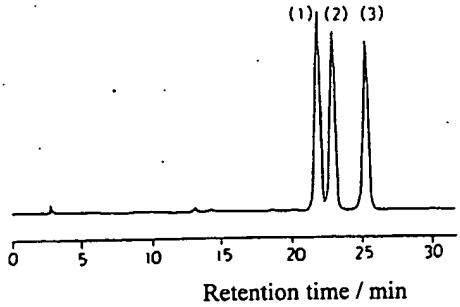


Figure 3



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